REMARKS

In view of the denial of entry of their Amendment mailed November 4, 2008, Applicants submit a Request of Continued Examination along with an Amendment that includes and elaborates upon the arguments presented in the Amendment that was not entered.

Applicants gratefully acknowledge withdrawal of the previous obviousness rejection under 35 U.S.C. 103(a) based on CA 2,474,902 ("Elbe et al") taken alone or in combination with JP 08/176112 ("Kanji et al") and the obviousness-type double patenting rejection based on copending application Serial No. 10/502,994.

Allowable Subject Matter

Applicants gratefully acknowledge the indication in the Final Office Action that Claims 26, 28, and 29 stand only objected to as being dependent upon a rejected base claim but would be allowable if rewritten in proper independent form. Applicants again note for the convenience of the Examiner that Claim 26 is directed to embodiments of Claim 18 in which R^6 represents $-COR^7$ in which R^7 is limited to 4-(difluoromethyl)-2-methyl-1,3-thiazol-2-yl; Claim 28 is directed to embodiments of Claim 18 in which R^6 represents -CHO; and Claim 29 is directed to embodiments of Claim 18 in which R^6 represents specific alkyl or substituted alkyl groups, cycloalkyl groups, or sulfanyl, sulfinyl, or sulfonyl groups but not carbonyl-containing groups within the meaning of $-COR^7$. Applicants maintain that all pending claims, including the base claim, are allowable as written and thus have not amended Claims 26, 28, and 29 as kindly suggested by the Examiner.

Declarations under 37 C.F.R. 1.132

The Final Office Action and by extension the Advisory Action continue to express a misunderstanding of the numbering scheme used for the compounds described in one of the two Declarations under 37 C.F.R. 1.132 of Dr. Ulrike Wachendorff-Neumann. Consequently, Applicants maintain that the conclusions expressed in the various Office Actions do not accurately reflect the correct meaning of their data.

Applicants again point out that the Final Office Action at pages 3-4, as well as page 11, incorrectly states that Table I of the first of these Declarations shows an incorrect structure or number label for "Example 2" and that the same error appears in the other tables. Applicants again emphasize that the Example numbers used in the first Declaration are simply a sequential listing of each test carried out according

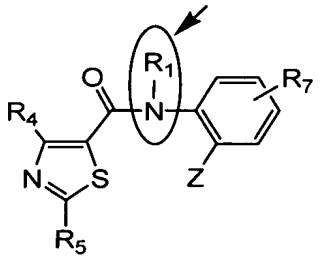
to the test protocols and reported in the Declaration – beginning with the first test described in the Declaration (i.e., Example 1 in Table I) and ending with the final test described in the Declaration (i.e., Example 8 in Table IV). That is, all of the example numbers identify only to the *tests* described in the Declaration, not the *compounds* that were tested. Applicants have never made a representation in either the Declaration or their Amendments that the numbers used in the Declaration were intended to correlate with any of the example numbers used in the examples in their specification (or in the reference). To the contrary, each Table of the first Declaration clearly shows that the odd-numbered examples refer to tests carried out on known compounds described in preparative examples of the cited references. and that the even-numbered examples refer to tests carried out on the inventive compound. The reason the same structure is displayed for all of the even-number examples in the tables of the first Declaration is that the same compound was used in all of these examples.

In short, Applicants' Example Set I of Dr. Wachendorff-Neumann's first Declaration shows a direct comparison between the compound of Example 9 of their invention and the compound of Example 4.32 of WO 02/059086 ("Walter et al"). The remaining Example Sets of the first Declaration and Example Sets I and II of the second Declaration compare the inventive compounds of Applicants' Examples 9 and 6, respectively, with other known compounds that, although not specifically disclosed in Walter et al, are probative of patentability as explained below.

Rejection under 35 U.S.C. 103

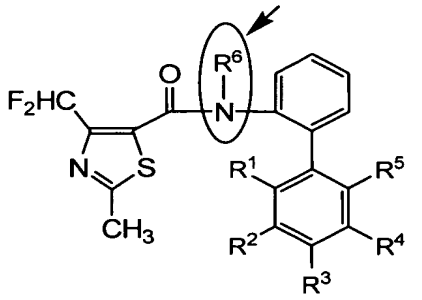
Claims 18-25, 27, and 29-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/059086 ("Walter et al"), taken alone or in combination with JP 08/176112 ("Kanji et al"). Applicants again respectfully traverse.

As fully discussed in Applicants' previous Amendments, **Walter et al** discloses certain microbicidal carboxamides, among the many types of which are compounds that can be represented by the formula



(which is not shown as such in the reference but is pieced together from the general disclosure where A is group (A3) and Q is group (Q1)) in which $\mathbf{R_1}$ (designated by an oval and arrow) can be one of three very specific unsaturated hydrocarbon groups having at least one carbon-carbon multiple bond or COR_3; $\mathbf{R_2}$ is hydrogen or any of several carbon-containing substituents; $\mathbf{R_3}$ is optionally substituted alkyl (in which the optional substituent can be halogen, alkoxy, or haloalkoxy) or is alkylthio, haloalkylthio, alkoxy, haloalkoxy, alkenyloxy, haloalkenyloxy, alkynyloxy, or haloalkynyloxy; $\mathbf{R_4}$ is optionally fluorinated methyl (including, among other groups, CF_3, CF_2H, and CFH_2) or is chlorine or bromine; $\mathbf{R_5}$ is methyl, CF_3, CH_2OCH_3, or CH_2OCF_3; and **Z** is phenyl or halophenyl, optionally substituted C_5-C_7 cycloalkyl, or a branched alkyl group. See pages 1-2. Walter et al thus encompasses compounds in which A is group (A3), Q is group (Q1), and the bridging amide group can bear a carbonyl group connected to a narrowly defined set of optionally substituted alkyl, alkoxy, alkylthio, alkenyloxy, or alkynyloxy groups (i.e., COR_3).

Applicants, on the other hand, claim thiazolylbiphenylamides of formula (I)



(I)

in which the bridging amide nitrogen atom (again shown by an oval and arrow) is substituted by either (1) non-carbonyl R^6 groups that are entirely different from the unsaturated hydrocarbon groups taught by Walter et al or (2) certain carbonyl-containing R^6 groups.

Applicants assume that the Final Office Action, by indicating that Claim 29 would be allowable if written in independent form, has effectively acknowledged that compounds of their invention in which R^6 represents non-carbonyl groups (such as alkyl groups) are patentably distinct from Walter et al (and, for that matter, from Walter et al in view of Kanji et al).

Applicants therefore direct attention to embodiments of their invention in which the amide substituent R^6 is the carbonyl-containing group $-COR^7$. Applicants maintain that such compounds are patentably distinct from the carbonyl-containing

compounds of Walter et al in which A is the thiazolyl group (A3), Q is the phenyl group (Q1), and the bridging amide group is substituted with COR_3 (as shown above). Applicants can further narrow their arguments with respect to the carbonyl-containing group $-COR^7$. *First*, the Final Office Action at page 11 has confirmed the allowability of claims that limit the carbonyl-containing substituents as specified in Claim 26 (in which R^6 represents $-COR^7$ to the extent that R^7 is limited to 4-(difluoro-methyl)-2-methyl-1,3-thiazol-2-yl) and Claim 28 (in which R^6 represents formyl) – and on the failure of Walter et al to disclose compounds in which its R_3 is an amino group (which would correspond to Applicants' compound when R^6 is $-CONR^8R^9$). *Second*, Walter et al does not include amino groups within the definition of its R_3, which means that the reference also would not suggest compounds of Applicants' invention in which R^6 is $-CONR^8R^9$.

With these established distinctions in mind, Applicants now address the remaining compounds of their invention in which R^6 encompasses carbonyl groups that are in some cases similar to the carbonyl group COR_3 of Walter et al (for example, where R_3 is (halo)alkyl or (halo)alkoxy). Applicants respectfully submit that when the overall teachings of the references are viewed in proper context, their claimed invention is patentably distinct from Walter et al, even when combined with Kanji et al.

It has long been recognized that even structurally similar inventions can be patentably distinct under certain circumstances. E.g., *U.S. v. Adams*, 383 U.S. 39, 148 U.S.P.Q. 479 (1966). For example, a claimed invention is not rendered obvious merely because a reference discloses "compounds having a generic formula which would include [the claimed compounds] if proper selection from among the many possible variables were made as suitable for the claimed purpose." *Ex parte Strobel and Catino*, 160 U.S.P.Q. 352 (P.O. Bd. App. 1968); see also *In re Baird*, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994). This principle is particularly applicable where the properties exhibited by compounds in the relevant art are unpredictable and where, as here, comparative evidence supports a finding of non-obviousness.

With respect to the claims now at issue, Applicants maintain that Walter et al does not describe the particular combination of structural features that characterize the N-carbonyl-substituted embodiments of Applicants' claimed invention nor does the reference show even one example of an N-carbonyl-substituted compound in which A is a thiazole bearing a haloalkyl substituent R_4 other than CF_3. Only by

improperly picking and choosing from the host of possible groups disclosed in the reference could one in hindsight arrive at Applicants' specified combination of features. That is, to arrive at Applicants' claimed compounds, it would be necessary to **(A)** select only thiazoles (A3) from among the five heterocyclic structures of group A and *even then* only thiazoles in which substituent R_4 is CF_2H and **(B)** select only phenyl groups (Q1) from among the six ring structures of group Q and *even then* only phenyl groups in which substituent Z is phenyl or halophenyl and **(C)** select only COR_3 from among seven specific possibilities for group R_1 and *even then* only when R_3 represents only certain groups. The reference provides no indication that such specific selections would provide enhanced properties.

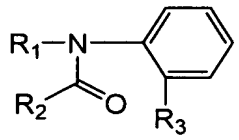
Applicants maintain that this failure of Walter et al to disclose compounds having the specific combination of features that characterize their invention is consistent with the patentability of their claimed invention. By way of further support, Applicants again refer to the previously presented Declarations of 37 C.F.R. 1.132 of Dr. Ulrike Wachendorff-Neumann, which (as discussed above) provide appropriate supporting data.

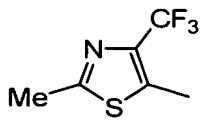
First, Example Set I of the first Declaration provides a direct comparison between the inventive compound of Applicants' Example 9 (which is shown in Table 1 at pages 40-41 of the specification) and the compound of Example 4.32 of Walter et al. In particular, Applicants' inventive compound of Example 9, which has both an N-carbonyl group on the amide bridge and a difluoromethyl substituent on the thiazole moiety, exhibited significantly enhanced biological activity compared to the known compound of Example 4.32 of Walter et al (see page 33), which, although having the same N-carbonyl substituent on the amide bridge, has a trifluoromethyl substituent instead of a difluoromethyl group on the thiazole moiety. The Final Office Action, however, states that the reference teaches the interchangeability of trifluoromethyl and difluoromethyl groups and that Applicants' data are insufficient to overcome the rejection.

Applicants again refer to the Dr. Wachendorff-Neumann's Declarations. With respect to the supposed teaching of interchangeability of trifluoromethyl and difluoromethyl groups, Applicants' data speak for themselves. It is well recognized that those skilled in the art would reasonably expect compounds having alternative substituents to exhibit essentially equivalent properties absent a clear teaching to the contrary. Walter et al teaches that group R_4 attached to the thiazole ring can be a methyl

group, any of several halogenated methyl groups (i.e., CF_2Cl, CF_3, CF_2H, or CFH_2), chlorine, or bromine, all of which would be assumed by those skilled in the art to confer essentially equivalent properties. Applicants, in contrast, have shown the significance of difluoromethyl substitution. It may also be noted that Walter et al provides no biological test data for any compound in which group A is a thiazolyl group (A3), which suggests that those skilled in the art would not be led to expect thiazolyl compounds to be preferred, regardless of the nature of the R_4 group. Applicants therefore again submit that Dr. Wachendorff-Neumann's first Declaration shows what it purports to show– that an inventive compound having a difluoromethyl substituent on the thiazole moiety is superior to a known comparison compound that differs only in having a trifluoromethyl substituent. Applicants also submit that the Final Office Action has provided no objective evidence to the contrary. Applicants therefore submit that their claimed invention is patentably distinct from Walter et al taken alone. Applicants also maintain that Kanji et al would not lead those skilled in the art to their claimed invention.

The Final Office Action at page 6 relies on Kanji et al, inter alia, as teaching the interchangeability of the various substituents at the amide nitrogen atom of the disclosed thiazole-containing carboxamides. Applicants respectfully that Kanji et al does not provide the necessary nexus between the teachings of Walter et al and their claimed invention. As already fully discussed in Applicants' previous Amendments, **Kanji et al** discloses carboxamides of the formula



in which $\mathbf{R_1}$ can be any of a number of groups, including acyl groups of formulas $-CO-R_4$ (where R_4 can be alkyl, haloalkyl, or phenoxymethyl) or a second amide moiety $-CO-NH-R_5$ (where R_5 can be alkyl or phenyl), as well as certain ethers R_6 or alkyl groups R_7; $\mathbf{R_2}$ can be a variety of cyclic groups, including a specific trifluoromethyl-substituted thiazole moiety having the formula  ; and $\mathbf{R_3}$ can be any of a variety of cyclic or unsaturated groups, including phenyl. However, regardless of whether Kanji et al teaches such interchangeability of amide substituents, the reference does not even remotely suggest that the thiazole moiety

could bear any haloalkyl substituent other than CF_3, which, as discussed above, Applicants have shown confers inferior properties relative to the CHF_2 group that characterizes their invention. In the absence of any suggestion of a difluoromethyl-substituted thiazolyl moiety, Kanji et al adds nothing that Walter et al does not already disclose that would lead those skilled in the art to their claimed invention.

In addition to the points addressed above, the Final Office Action at page 3 states that Applicants should have provided more data for more compounds. More particularly, the Final Office Action refers to Applicants' Examples 1 and 8 (in which R^6 is acetyl) and Example 9 (in which R^6 is methoxyacetyl) and suggests that Applicants should have augmented their arguments by comparing these inventive compounds to Compound 4.20 (in which R_1 is acetyl) and Compounds 4.43 and 4.44 (in which R_1 is methoxycarbonyl, not methoxyacetyl) of Walter et al. [Applicants also note that the Final Office Action later refers to Compound 7.03 of the reference, which is not a thiazolyl compound and thus has little if any relevance to the claims at issue.] Aside from the fact that the structural difference between a methoxyacetyl group (as in Applicants' Examples 1 and 8) and a methoxycarbonyl group (as in Compounds 4.43 and 4.44 of Walter et al) means that a comparison between Applicants' Example 9 and Compound 4.43 or 4.44 of the reference would have questionable value, Applicants maintain that the direct comparison of their inventive Example 9 with Compound 4.32 of the reference as described in Example Set I of Dr. Wachendorff-Neumann's first Declaration is at least as representative and relevant as any other comparison suggested in the Final Office Action. The purpose of the comparison experiment described in Example Set I of the first Declaration was not to show the biological effect of different kinds of amide substituents R^6 – that was the purpose of other experiments carried out by Applicants and discussed below – but instead was to show the effect of substitution in the thiazole ring by a difluoromethyl group compared to a trifluoromethyl group. Because Applicants' directly comparative experiments show the significance of difluoromethyl substitution of the thiazole moiety, Applicants submit that another test using any other such compound of the reference, particularly with respect to substitution on the bridging amide, would be essentially duplicative and unnecessary.

Nevertheless, Applicants have also shown the significance of the amide substituents defined for their group R^6 by comparing inventive compounds in which R^6 is methoxyacetyl or methyl with unsubstituted amides (i.e., where R^6 would be H)

that are outside the scope of their claims. Because the tested compounds are characterized by a difluoromethyl group attached to the thiazole ring (a feature not exemplified for thiazoles according to Walter et al), they are not directly comparative with Compounds 4.43 and 4.44 of the reference, which have only a trifluoromethyl group attached to the thiazole ring. Nevertheless, because the comparisons focus on only one structural difference (i.e., amide substitution), the data shown for Example Sets II through IV of the first Declaration and Example Sets I and II of the second Declaration are at least as probative as the experiments suggested in the Final Office Action. Furthermore, even if these experiments are only indirectly comparative with compounds found in Walter et al, it is well established that even indirect comparisons, when "based on established scientific principles, can validly be applied to distinguish a claimed chemical process or product from that disclosed in the prior art." *In re Best, Bolton and Shaw*, 562 F.2d 1529, 195 U.S.P.Q. 430, 432 (C.C.P.A. 1977); see also *In re Blondel, Fouche, and Gueremy*, 499 F.2d 1311, 182 U.S.P.Q. 294 (C.C.P.A. 1974). Applicants respectfully submit that they have presented evidence that shows that their invention is distinguishable from Walter et al.

More specifically, Dr. Wachendorff-Neumann's Declarations show that two inventive compounds in which the bridging amide function bears a carbonyl-containing substituent within the meaning of Applicants' R^6 group are uniformly superior to two corresponding known compounds in which the bridging amide function is unsubstituted (which, it may be noted by way of comment, are disclosed in CA 2,474,902, the "Elbe et al" reference cited in the withdrawn obviousness rejection mentioned above). In particular, Applicants' Example Sets II through IV of the first Declaration show that Applicants' compound of Example 9 (in which R^6 is methoxyacetyl and the biphenyl substituent R^3 is chlorine) and Example Sets I and II of the second Declaration show that Applicants' compound of Example 6 (in which R^6 is methyl and the biphenyl substituent R^3 is bromine) are superior to their unsubstituted amide counterparts represented by Examples 21 and 2, respectively, of Elbe et al.

In short, Applicants have shown the superiority of compounds having a combination of at least three distinguishing features, specifically, a difluoromethyl substituted thiazole moiety and a substituted amide bridge. Applicants maintain that this particular combination of features confers enhanced activity against micro-organisms not within the contemplation of the cited references.

Applicants therefore respectfully maintain that their invention is not rendered obvious by Walter et al, whether taken alone or in combination with Kanji et al.

In view of the preceding amendments and remarks, allowance of the claims is respectfully requested.

Respectfully submitted,

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